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Leptin differentially remodels vertebrae and tibia trabecular bone independent of load *in vivo*

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Leptin is a 166AA adipokine predominantly secreted by adipocytes. Circulating leptin concentrations are determined chronically by the volume of adipose tissue and acutely by fluctuations in food intake. Leptin contributes to energy metabolism, acting to reduce appetite and body weight as well as increased heart rate and blood pressure, however the effects of leptin on bone metabolism remain contradictory. In this study high resolution μ CT (SKYSCAN 1272) was used to scan and analyse vertebrae and tibia samples collected from leptin deficient Ob/Ob mice (n=4), which were weight matched with c57 controls (n=4), from 4-22 weeks of age. Bone samples were scanned at a resolution of 4.3 μ m, 0.7° rotation step and reconstructed using NRecon. Post-reconstruction, CTAn was used to calculate percentage trabecular bone volume (BV/TV), trabecular thickness (Tb.Th.), trabecular number (Tb.N) structural model index (SMI), bone mineral density (BMD) and cortical bone volume (C.BV). BV/TV of the Ob/Ob tibias was significantly decreased compared to c57 controls (12.73 ± 0.73 vs 7.81 ± 0.91 , respectively) (Figure 1a). Compared to c57, Ob/Ob mice tibia had a significant reduction in trabecular thickness: $0.043 \pm 0.001\text{mm}$ vs. $0.037 \pm 0.001\text{mm}$ (Figure 1c), and number: $3.19 \pm 0.21\text{mm}^{-1}$ vs. $2.09 \pm 0.22\text{mm}^{-1}$ (Figure 1d), respectively. Furthermore, Ob/Ob mice tibia trabeculae showed a significant increase in SMI (2.07 ± 0.07) compared to c57 (1.83 ± 0.09), demonstrating tibia trabeculae were becoming more rod like (Figure 1b), indicative of increased osteoclast activity. Similar trends were observed in the trabeculae of c57 and Ob/Ob vertebrae samples for BV/TV, T.Th., however vertebrae T.N. was not significantly reduced in Ob/Ob mice compared to c57 controls ($6.47 \pm 0.20\text{mm}^{-1}$ to $5.99 \pm 0.20\text{mm}^{-1}$, respectively) (Figure 2). Cortical BV of the tibia was reduced in Ob/Ob compared to c57 controls ($0.72 \pm 0.01\text{mm}^3$ to $0.60 \pm 0.02\text{mm}^3$, respectively) (Figure 3). In all samples analysed, BMD did not significantly differ between weight-paired Ob/Ob and c57 controls, demonstrating leptin deficiency, independent of load, did not affect density of trabecular or cortical bone. However, findings on thickness, percentage bone volume and SMI suggest leptin plays a significant role in promoting bone resorption and/or inhibiting bone formation in both trabecular and cortical

areas, and that this occurs differentially between the spine and long bones independent of weight.

